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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/724,727	12/02/2003	Dexiang Chen	036481-0143	2185

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EXAMINER	
CHEN, STACY BROWN	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 01/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/724,727	CHEN ET AL.	
	Examiner	Art Unit	
	Stacy B Chen	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *24-29* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 30-35* is/are rejected.

7)☒ Claim(s) *1-23 and 30-35* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/2/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the response filed November 17, 2004, Applicant's election of Group II, claims 1-23 and 30-35 with respect to the embodiment wherein the vaccine composition is a nucleic acid, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 1-35 are pending. Claims 1-23 and 30-35 are under examination. Claims 24-29 are withdrawn from consideration, being drawn to non-elected inventions.

Specification

2. The specification is objected to for the following informality: The priority data information on the first page of the specification must be updated with regard to the status of parent application 09/710,104, now abandoned.

Claim Objections

3. Claims 1-23 and 30-35 are objected to for reciting a non-elected invention, specifically, a vaccine composition that is an antigen. Accordingly, independent claim 1 should be amended to recite, "wherein the vaccine composition comprises a nucleic acid encoding an antigen". Likewise, claim 30 and dependent claims 30-33 recite a non-elected claim and should be written in independent form. Further, claim 8 appears to be particular to the non-elected invention encompassing an antigen, not a nucleic acid encoding an antigen because claim 8 encompasses an antigen that is a live, attenuated organism. In order to administer a nucleic acid encoding a live, attenuated organism, the method would require more steps to enable the formation of a live,

attenuated organism following nucleic acid administration. Clarification regarding the subject matter of claim 8 is requested.

Claims 1-23 and 30-35 recite the limitation, "into or across the skin". The meaning of "into the skin" versus "across the skin" appears to be redundant. Is the distinction that "into the skin" means into one of the layers of skin, or between the layers or skin, while "across the skin" means injection beyond the innermost side of skin, or spread topically? Clarification is requested.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-35 are rejected under 35 U.S.C. 112, first paragraph. The specification is enabling for a method of treating a disease caused by the entry of a pathogen into the body of a subject via a mucosal surface, comprising delivering a nucleic acid particulate vaccine composition to a subject. However, the specification does not reasonably provide enablement for preventing a disease using a nucleic acid particulate vaccine. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The breadth of the claims encompasses the treatment of a disease comprising administering a particulate vaccine composition comprising nucleic acid that encodes a vaccine antigen. According to the specification, treatment of a disease is defined as prevention of

infection or reinfection, reduction or elimination of symptoms, and the reduction or complete elimination of a pathogen (pages 13-14, bridging paragraph). The Office is making a distinction between treatment and prevention, wherein treatment is an improvement of some aspect of the disease, whereas prevention is the complete avoidance of disease. The nature of the invention is the administration of particulate nucleic acid vaccine compositions which result in encoded polypeptides that treat or prevent a disease.

The state of the art surrounding DNA vaccines generally shows that naked DNA vaccines administered *in vivo* in conjunction with adjuvants such as CpG motifs are able to stimulate the immune system better than DNA by itself or *in vitro*, pages 4-5, bridging paragraph of Kim *et al.* (*Arch. Pharm. Res.* 2001, 24(1):1-15). Kim *et al.* is relevant to the state of the art in that the instant claims are not limited to needleless syringe powder injection, but encompass needle injection of a particulate vaccine. (See claims 30 and 31 which only require general administration and only recite that the composition is "suitable" for transdermal application. See also claims 32, 34 and 35, which require transdermal application, but not specifically needleless syringe injection.) Kim *et al.* discloses that administration of particulate non-viral delivery systems is easily eliminated by reticuloendothelial systems (page 2, first column, first full paragraph). Also discussed briefly are gene gun techniques that deliver the genes into cytoplasm, thus having a greater chance of gene expression (page 6, second column, first paragraph). Poland *et al.* (*BMJ*, 2002, 324:1315-1319) teach that "intramuscularly injected DNA in humans has failed to generate vigorous immune responses, although transdermal or intradermal delivery of DNA has been more encouraging", page 1315, bottom of first column. With regard to transcutaneous application, Poland *et al.* discloses that animal studies have shown

production of systemic and mucosal antibodies after topical vaccine application (page 1317, middle of second column). Eo *et al.* (*J. Immunol.* 2001, 166 :5473-5479) disclose a prime-boost immunization with a DNA vaccine in plasmid form and in a viral vector. Eo *et al.* found that systemic prime-boost with herpes simplex virus glycoprotein B DNA failed to induce humoral or T cell responses at mucosal sites, but if the DNA was administered at a mucosal site (both prime and boost, or prime followed by systemic boost), proximal and distal locations showed mucosal responses (abstract). The state of the art shows that DNA immunization is progressing, but still faces obstacles when attempting to prevent disease.

The level of skill in the art is high, evidenced by the references discussed above relating to the state of the art. The amount of guidance or direction present in the specification does not account for the lack of predictability in the prevention of disease with DNA vaccines. The specification provides the materials and how to prepare the materials for administration, but fails to show that DNA particulate vaccines will overcome the deficiencies in the art relating to prevention of disease. The examples in the specification are directed to antigen vaccines (proteins), however there are no examples of DNA vaccines that attain a level of expression sufficient to prevent infection. It would require undue experimentation to use DNA particulate compositions to demonstrate prevention of disease without having the appropriate animal models and challenge experiments. Therefore, given the breadth of the claims, the state of the art at the time of the invention, the nature of the invention, the high level of one of ordinary skill in the art, the low level of predictability in the art, the lack of guidance provided in the specification and working examples particular to DNA, and the undue quantity of experimentation required to use the invention, the claims are not enabled for their full scope.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7 are rejected under 35 U.S.C. 102(b) as being anticipated by Burkoth *et al.* (WO 98/10750, herein, "Burkoth"). The claims are drawn to a method of generating a mucosal immune response at a mucosal surface, said method comprising delivering a particulate vaccine composition into or across the skin of a vertebrate subject using a transdermal delivery technique, wherein the vaccine composition comprises a nucleic acid encoding an antigen. According to the specification, a mucosal immune response is induction of a cellular and/or humoral immune response against an antigen or infection at a mucosal surface (page 11). The response is specific for the antigen and is characterized by an IgA antibody response. (Mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. Secretory IgA is found in intestinal secretions, respiratory secretions, saliva and tears for example.) According to the specification, mucosal surfaces include the intestinal tract, respiratory tract, urogenital tract (reproductive tract) and the eyes (page 11, lines 10-14). According to the specification, transdermal delivery includes intradermal (into the skin) and transdermal delivery (applied to the top layer of the skin), pages 9-10, bridging paragraph. Specifically, the composition is administered with a needleless syringe injection device. The

antigen is derived from or obtained from a pathogen that enters a subject's body via a mucosal surface, such as a viral or bacterial pathogen.

Burkoth discloses transdermal (percutaneous) and transmucosal administration of drugs and pharmaceuticals, wherein the drugs and pharmaceuticals are in dry particulate form (page 10, line 32 through page 11, line 19, and page 19, lines 9-11). The administration is via needleless injection using powdered nucleic acid molecules (Burkoth claims 11-13, and page 1, lines 10-14). Burkoth's method includes nucleic acid immunizations to the stratum basal layer of skin (page 6, lines 3-8). The nucleic acid encodes an immunogenic sequence that serves to elicit a humoral and/or cellular immune response in a subject (page 13, lines 12-16). The nucleic acid sequences encode peptides known to display antiviral and/or antibacterial activity (page 14, lines 16-19). Since the materials and methods of Burkoth and Applicant are the same, namely transdermal delivery of nucleic acid using a needeleless syringe, the outcome of generating a mucosal immune response at a mucosal surface is expected. Further, since a mucosal immune response is expected as a result of Burkoth's method, an antigen specific IgA response would also be expected. An antigen specific immune response would be expected because mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. In order for the IgA to provide immunity, it must be specific for that particular invading pathogen/antigen. Therefore, the claims are anticipated by Burkoth.

6. Claims 1, 3-5, 9-14 and 16-19 are rejected under 35 U.S.C. 102(b) as being anticipated by Sato *et al.* (*Science*, 1996, 273:352-354, herein, "Sato"). The claims are drawn to a method of generating a mucosal immune response at a mucosal surface, said method comprising delivering

a particulate (having particles) vaccine composition into or across the skin of a vertebrate subject using a transdermal delivery technique, wherein the vaccine composition comprises a nucleic acid encoding an antigen. According to the specification, a mucosal immune response is induction of a cellular and/or humoral immune response against an antigen or infection at a mucosal surface (page 11). The response is specific for the antigen and is characterized by an IgA antibody response. (Mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. Secretory IgA is found in intestinal secretions, respiratory secretions, saliva and tears for example.) According to the specification, mucosal surfaces include the intestinal tract, respiratory tract, urogenital tract (reproductive tract) and the eyes (page 11, lines 10-14). According to the specification, transdermal delivery includes intradermal (into the skin) and transdermal delivery (applied to the top layer of the skin), pages 9-10, bridging paragraph. The antigen is derived from or obtained from a pathogen that enters a subject's body via a mucosal surface. Also claimed are methods wherein an adjuvant composition is administered in particulate form. The adjuvant and vaccine composition are administered to the same site, or concurrently, or in a combined composition.

Sato discloses the administration of plasmid DNA expression vectors that encode proteins and induce long-lasting cellular and humoral immune response via intramuscular and intradermal delivery. Sato also teaches that immunostimulatory DNA sequences are necessary for effective intradermal gene immunization (abstract and page 354, second column, last paragraph). In particular, Sato designed a vector that encodes CpG sequences in addition to a sample antigen sequence, beta-galactosidase. Sato found that intradermal injection of the vector comprising CpG and the antigen elicited strong humoral and cellular immune responses to the

antigen (last paragraph of page 352 through page 353). While the vector composition is not explicitly called a "particulate" composition, Sato's composition comprised particles containing the vector. Sato's administration of the vector resulted in administration of the adjuvant and antigen to the same site, concurrently, and in a single composition. Since the materials and methods of Sato and Applicant are the same with regard to the transdermal delivery of nucleic acid, the outcome of generating a mucosal immune response at a mucosal surface is expected. Further, since a mucosal immune response is expected as a result of Sato's method, an antigen specific IgA response would also be expected. An antigen specific immune response would be expected because mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. In order for the IgA to provide immunity, it must be specific for that particular invading pathogen/antigen. Therefore, the claims are anticipated by Sato.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Burkoth in view of Kaiserlian *et al.* (*European J. Dermatology*, 1999, 9(3):169-176, herein, "Kaiserlian", web page printout pages 1-6). Claim 15 is drawn to a method of generating a mucosal immune response at a mucosal surface, said method comprising delivering a particulate vaccine composition and adjuvant into or across the skin of a vertebrate subject using a transdermal

delivery technique, wherein the vaccine composition comprises a nucleic acid encoding an antigen. Specifically, the vaccine composition comprises an adjuvant and vaccine component. The composition is administered using a needleless syringe powder injection device.

Burkoth discloses transdermal (percutaneous) and transmucosal administration of drugs and pharmaceuticals, wherein the drugs and pharmaceuticals are in dry particulate form (page 10, line 32 through page 11, line 19, and page 19, lines 9-11). The administration is via needleless injection using powdered nucleic acid molecules (Burkoth claims 11-13, and page 1, lines 10-14). Since the materials and methods of Burkoth and Applicant are the same, namely transdermal delivery of nucleic acid using a needeleless syringe, the outcome of generating a mucosal immune response at a mucosal surface is expected. Further, since a mucosal immune response is expected as a result of Burkoth's method, an antigen specific IgA response would also be expected. An antigen specific immune response would be expected because mucosal immune responses are characterized by the presence of secretory IgA that provides local immunity. In order for the IgA to provide immunity, it must be specific for that particular invading pathogen/antigen. Burkoth does not teach the use of an adjuvant in combination with the vaccine component.

However, Kaiserlian teaches that effective intradermal immunization with DNA requires immunostimulatory sequences, such as CpG (page 3 of webpage printout, second full paragraph). Kaiserlian discloses that DNA vaccines administered in saline are effective without the need for adjuvants or delivery systems, however, intradermal immunizations with DNA have different requirements for an effective immune response. One of ordinary skill in the art would have been motivated to administer an adjuvant with Burkoth's powder vaccine because

Kaiserlian's teaches that effective intradermal immunization with DNA requires immunostimulatory sequences. One would have been motivated to supplement the powder vaccine of Burkoth with CpG nucleotides in order to stimulate a greater immune response. Administering the adjuvant with the vaccine would have been obvious because Kaiserlian teaches that immunostimulatory sequences are often part of the plasmid that contains the vaccine nucleic acid sequence, expressed at the same time. One would have had a reasonable expectation of success that a plasmid containing immunostimulatory sequences, such as Kaiserlian's CpG motifs, along with a vaccine nucleic acid sequence of Burkoth, would have worked as an immunization to generate a mucosal immune response. Therefore, the claims are obvious over Burkoth in view of Kaiserlian.

8. Claims 20-23 and 30-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burkoth in view of Kaiserlian, as applied to claim 15 above, and further in view of McCluskie *et al.* (*J. Immunol.* 1998, 161:4463-4466, herein, "McCluskie"). The claims are drawn to a method of generating a mucosal immune response at a mucosal surface, said method comprising delivering a particulate vaccine composition and adjuvant(s) into or across the skin of a vertebrate subject using a transdermal delivery technique, wherein the vaccine composition comprises a nucleic acid encoding an antigen. The mucosal immune response is specific for the antigen. Also claimed is a method of treating a disease caused by the entry of a pathogen into the body of a vertebrate subject via a mucosal surface, said method comprising administering a vaccine composition comprising a particulate vaccine composition suitable for delivery into or across skin of a vertebrate subject comprising a nucleic acid encoding an antigen, an ADP-

ribosylating toxin and an oligonucleotide containing a CpG motif. (The embodiment of preventing disease with DNA immunization is not included in this rejection because it is currently considered a non-enabled embodiment.) Specifically, the particulate vaccine composition is delivered using a needleless syringe powder injection device.

The teachings of Burkoth and Kaiserlian are summarized above. Burkoth and Kaiserlian are silent on the administration of an additional adjuvant, such as CT with CpG motifs.

However, McCluskie discloses that the mucosal adjuvant, cholera toxin (CT) is often used with subunit vaccines and demonstrates synergistic effects on both the humoral and cellular immune responses against the vaccine antigen when administered together with CpG motifs (abstract). McCluskie administers hepatitis B surface antigen by nasal inhalation concurrently with CT and CpG (page 4464, column 1, first paragraph).

It would have been obvious to modify the method of Burkoth by co-administering adjuvants. One would have been motivated to include CpG sequences, as taught by Kaiserlian, and to further include CT because McCluskie teaches that CT and CpG act synergistically to generate both mucosal and systemic immune responses. Although McCluskie does not administer the CT and CpG with a nucleic acid component, the nucleic acid of Burkoth/Kaiserlian (encoding an antigen and CpG), would have been expected to be expressed, at which point the mucosal adjuvant effect of the CT and CpG would have taken effect. One would have had a reasonable expectation of success because McCluskie demonstrates that CT and CpG induced act synergistically to induce a systemic and mucosal immune response against a hepatitis B surface antigen. Therefore, the claims are obvious over Burkoth in view of Kaiserlian and further in view of McCluskie.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

9. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stacy B. Chen whose telephone number is 571-272-0896. The examiner can normally be reached on M-F (7:00-4:30). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James C. Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Stacy B. Chen

Stacy B. Chen
January 18, 2005